mini-proinsulin in a native conformation [thereby producing mini-proinsulin]; and

(c) incubating the mini-proinsulin of step (b) with trypsin [under slightly acidic conditions] at a pH of about 6.8 [where phenol and other similar aromatics are not present] under conditions where no crystals are formed.

REMARKS

Reexamination and reconsideration of this application are respectfully requested.

Applicants respectfully request that this Amendment be entered pursuant to 37 C.F.R. § 1.116(a). Applicants submit that this Amendment places this application in condition for allowance or in better form for appeal. Moreover, several of these amendments render moot previous rejections and objections, and no new claims have been added.[1/] Following entry of this Amendment, claims 21-23, 25-27, and 29-30, as amended, will be pending in this application.

The Examiner objected to claims 18, 21-22, and 29 for failing to include the formula for formula I. In support of this objection, the Examiner notes that "[a] claim should be self-contained and not require reference to the specification." (Paper No. 22 at 2.) Applicants respectfully traverse this objection.

It is well established that claims are read in light of the specification. Since formula I is unambiguously identified in the

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1/ Exemplary support for the amendments to the claims can be found in the specification, inter alia, at page 3, line 28 to page 4, line 18; and at page 14, line 10 to page 16, line 8.

specification, applicants submit that no ambiguity results from the omission of formula I from the claims. Nevertheless, in an effort to advance the prosecution of this case, applicants have cancelled claim 18 and amended claims 21-22, and 29 to explicitly include formula I within these claims. Since this amendment renders the Examiner's objection moot, the withdrawal of this ground for rejection is respectfully requested.

The Examiner rejected claim 17 under the judicially-created doctrine of obviousness-type double patenting for allegedly being unpatentable over claim 17 of U.S. Patent 5,227,293 [hereinafter "the '293 patent"]. Applicants respectfully traverse this ground for rejection.

In In re Braat, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991), the Court of Appeals for the Federal Circuit considered whether a two-way obviousness determination was required to support an obviousness-type double patenting rejection in certain fact situations. The Court held that when a later-filed patent application issues prior to an earlier-filed application, the later-filed but earlier-issued application cannot form the basis of an obviousness-type double patenting rejection unless a two-way obviousness determination is performed. In re Braat at 1292-93.

In situations where a two-way test for obviousness-type double patenting applies, the Examiner must make two showings to meet her initial burden of establishing a prima facie case of unpatentability. First, the Examiner must establish that the subject matter of the claims being rejected would have been obvious over the cited patent. Secondly, the Examiner must also

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show that the subject matter being claimed in the cited patent would be obvious over the subject matter of the rejected claims.

The '293 patent issued from an application filed on August 29, 1989. In contrast, the earliest U.S. filing date for the present application is June 21, 1989.[2/] Therefore, the '293 patent was later-filed but earlier-issued and the holding in In re Braat controls. The Examiner is consequently required to establish obviousness-type double patenting using a two-way test.

In making this rejection, the Examiner provides reasons to support the allegation that the invention as instantly claimed is obvious in view of claim 17 of the '293 patent. (Paper No. 19 at 2.) Applicants contend that this conclusion of obviousness is unsupportable. (See Amendment of March 25, 1994 at 7-8.) However, the Examiner has not provided any reasons to support the reverse determination, i.e., that the invention of claim 17 of the '293 patent is obvious in view of the instantly claimed invention.

Since a two-way test for obviousness-type double-patenting has not been performed, this showing is insufficient to support the Examiner's rejection. Nevertheless, applicants have cancelled claim 17, without prejudice, rendering this rejection moot. Therefore, applicants respectfully request the Examiner to withdraw this ground for rejection.

The Examiner has objected to the specification under 35 U.S.C. § 112, first paragraph, and rejected claims 21-23, 25-27, and 29-30, alleging that the specification does not provide

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2/ This application is a continuation of Serial No. 07/369,686 filed June 21, 1989.

support for the invention as is now claimed. The Examiner contends that recitations in the pending claims concerning "[i]ncubating the compound of formula I with trypsin under slightly acidic conditions at a pH of about 6.8 where phenol and other similar aromatics are not present" are not supported by the specification. (Paper No. 22 at 3.) Applicants respectfully traverse this ground for rejection.

It is well established that the specification need not describe the claimed invention using the identical words found in the claims in order to satisfy the requirements of 35 U.S.C. § 112. Martin v. Johnson, 172 U.S.P.Q. 391, 395 (C.C.P.A. 1972). See also Kennecott Corp. v. Kyocera International, Inc., 5 U.S.P.Q.2d 1194, 1197 (Fed. Cir. 1987). Therefore, if a person of ordinary skill in the art would conclude that the recitations in the pending claims would be apparent from the specification, such recitations are supported even if they are not found in ipsis verbis in the specification.

Applicants contend that the recitations noted by the Examiner are either explicitly recited in the specification or would be apparent to one of ordinary skill in the art from the specification. For example, applicants explicitly teach a pH of 6.8 at page 15, line 24.

Moreover, teachings in the working examples imply conditions for trypsin cleavage to a person of ordinary skill in the art. In Example 4, at pages 15-16, trypsin digestion, converting mini-proinsulin to mono-Arg-insulin, takes place in an aqueous buffer,

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which does not contain phenol and similar aromatics.[3/] Following incubation with trypsin, the resultant mono-Arg-insulin is precipitated with $ZnCl_2$.[4/] The need to precipitate the trypsin digestion product would indicate to one of ordinary skill in the art that the trypsin digestion occurs in solution. Therefore, the specification implicitly teaches trypsin digestion under conditions where no precipitate, e.g. crystals, is formed.

Further teachings in the specification would indicate to one of ordinary skill that trypsin digestion cannot occur in solution if the digestion buffer contains phenol. Following digestion and precipitation, the mono-Arg-insulin is purified by crystallization. The specification teaches that crystallization is carried out using a buffer containing phenol. (Specification at 16, lines 3-6.) Since a crystal is a type of highly ordered precipitate and phenol crystallizes the mono-Arg-insulin digestion product, one of ordinary skill in the art would conclude that trypsin digestion in the presence of phenol could not be carried out in solution. Therefore, the specification implicitly supports trypsin digestion in the absence of phenol.

Nevertheless, in an effort to advance the prosecution of this case, and not in acquiescence to the Examiner's rejection, the pending claims have been amended to recite "under conditions where no crystals are formed." As discussed supra, support for this

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3/ In other working examples, phenol and other aromatic compounds are not used during trypsin digestion. (See Specification at 21, lines 13-16.)

4/ Further evidence that $ZnCl_2$ precipitates the mono-Arg insulin can be found in the specification at page 21, lines 27-30. (See also specification at 22, lines 3-5.)

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amendment can be found, inter alia, in the specification in Example 4 at pages 15-16. This working example teaches trypsin digestion carried out in solution, i.e., under conditions where no crystals are formed. Consequently, applicants submit that their invention as instantly claimed is fully supported by the specification as originally filed and respectfully request the Examiner to withdraw this ground for rejection.

The Examiner has rejected claims 17, 21-23, and 28-29 under 35 U.S.C. § 112, first paragraph, alleging that the disclosure is enabling only for claims limited to the production in bacteria of fusion proteins. Applicants respectfully traverse this ground for rejection.

The specification clearly discloses to one of ordinary skill in the art, expression of the mini-proinsulin as instantly claimed in native form or as part of a fusion protein. For example, the specification teaches, at page 2, lines 21-28, that a compound of formula I (mini-proinsulin) can be initially expressed free of any fusion protein. Moreover, Examples 8 and 9, at pages 20-21 of the specification, provide detailed experimental teachings concerning the expression of mini-proinsulin in native form, without first expressing the mini-proinsulin as part of a fusion protein.

Nevertheless, solely to expedite the prosecution of this application and not in acquiescence to the Examiner's rejection, applicants have cancelled claims 17 and 28 and amended the other rejected claims to relate to methods of expressing mini-proinsulin as part of a fusion protein. In light of these arguments and

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amendments to the claims, applicants respectfully request the Examiner to withdraw this ground for rejection.

The Examiner rejected claim 17 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner contends that "[c]laim 17 is confusing because it implies that formula I represents more than one compound in reciting 'if the gene structure also encodes for a fusion protein.'" (Paper No. 22 at 4.) Since claim 17 has been cancelled, this rejection has been rendered moot.

The Examiner also rejected claim 28 under 35 U.S.C. § 112, second paragraph, for being indefinite, alleging that "[c]laim 28 is confusing because it implies that formula I represents more than one compound in reciting 'compound of formula I is part of a fusion protein.'" (Id.) Since applicants have cancelled claim 28 without disclaimer or prejudice, this rejection has also been rendered moot. Therefore, applicants respectfully request that these rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

The Examiner rejected claims 16 and 18-20 under 35 U.S.C. § 103 for allegedly being unpatentable over either Markussen (U.S. Patent 4,916,212) or Markussen (EPO 163,529) [hereinafter collectively referred to as "the Markussen patent publications"]. In making this rejection, the Examiner alleges that the generic formula taught by Markussen, '212 patent at col. 2-3, encompasses

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applicants' claimed composition. (Paper No. 19 at 4.) Applicants respectfully traverse this ground for rejection.

It is well established that merely because a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. In re Jones, 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992). For the reasons advanced in the Amendment filed March 25, 1994, applicants contend that the generic disclosure of Markussen does not render the claimed invention obvious.

Nevertheless, solely to advance the prosecution of this case and not in acquiescence to the Examiner's rejection, applicants have cancelled claims 16 and 18-20 without disclaimer or prejudice, and expressly reserve the right to prosecute these claims in this or a continuing application. Therefore, this rejection has been rendered moot and its withdrawal is respectfully requested.

The Examiner rejected claims 17, 20, and 28 under 35 U.S.C. § 103 for being unpatentable over the Markussen patent publications in view of Goeddel. (Paper No. 22 at 5.) Applicants respectfully traverse this ground for rejection.

As discussed supra, neither of the Markussen patent publications teaches the mini-proinsulin as recited in the rejected claims. These deficiencies are not remedied by the teachings of Goeddel. Goeddel relate to mini-proinsulins containing a linking region, i.e., "C" chain or bridging chain, of two or more amino acids. Goeddel at 8, lines 20-22. In contrast,

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applicants' invention as instantly claimed relates to a mini-proinsulin containing a single arginine bridging the A and B chains. Therefore, none of the prior art relied upon by the Examiner teaches, either singly or in combination, all elements of the claimed invention. Nevertheless, solely to advance the prosecution of this case and not in acquiescence to the Examiner's rejection, applicants have cancelled claims 17, 20, and 28 without disclaimer or prejudice. Therefore, this rejection has been rendered moot, and applicants respectfully request the Examiner to withdraw this ground for rejection.

The Examiner also rejected claim 24 under 35 U.S.C. § 103 for allegedly being unpatentable over the Markussen patent publications either in view of Goeddel et al. and Mai et al. (Paper No. 22 at 6.) Applicants respectfully traverse this ground for rejection.

The invention as claimed in claim 24 relates to a fusion protein comprising a mini-proinsulin. As discussed supra, neither of the Markussen patent publications nor Goeddel teach this mini-proinsulin. Since the teachings of Mai do not relate to insulin or proinsulin, this article does not remedy this deficiency. As none of the cited art, either together or in combination, teaches applicants' invention as instantly claimed, the Examiner has failed to establish a prima facie case of obviousness. Nevertheless, solely to advance the prosecution of this case and not in acquiescence to the Examiner's rejection, applicants have cancelled claim 24 without disclaimer or prejudice. Therefore,

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this ground for rejection has been rendered moot and should be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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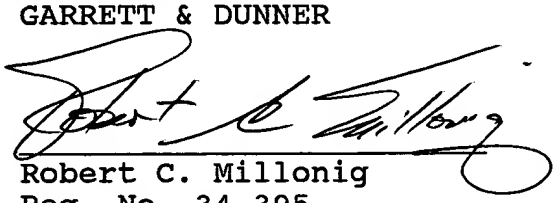
By: 
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